PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and Risk Factors Associated with Prehypertension in Shunde District, Southern China
AUTHORS	Xu, Dingli; Huang, Yuli; Qiu, Wenke; Liu, Changhua; Zhu, Dingji; Hua, Jinghai; Cai, Xiaoyan; Wu, Yanxian; Hu, Yunzhao

VERSION 1 - REVIEW

REVIEWER	Kelsi Anderson Baylor College of Medicine, USA
REVIEW RETURNED	20-Sep-2014

GENERAL COMMENTS	In this paper Huang et al. report the prevalence and risk factors of prehypertension in southern China. They conclude that prehypertension is highly prevalent in southern China. In addition, there was heterogeneity of combined risk factors within the prehypertensive subgroups. Although data are from a geographic area, I believe it is relevant for most clinicians worldwide, and the findings may have implications for decision-making in relation to prevention of hypertension and cardiovascular disease. I only have several comments for consideration: 1. Abstract-Design: The authors stated that this is "a cross-sectional study…. ". However, according to the methods in the main text, this is a retrospective study, using the community-based health checkup information. 2. Method: "The study information was collected in the First People's Hospital of Shunde"…"This study was approved by the Ethics Committee of the Affiliated Hospital at Shunde of the Southern Medical University " Are the statements indicating the same hospital? If yes, please make the statements consistent. 3. Results: As presented in table 1, the prevalence of prehypertension in female with 50–64 years was 36.3%, and 34.4% in those with ≥ 65 years old. I think this is very similar, and maybe it is not proper to state that "there was an increasing trend of prehypertension prevalence associated with age in men, but in women, the prevalence of prehypertension increased up to the age of 50–64 years and then decreased", especially in the case that linear correlation analysis was not performed. 4. Results: page 9, line 19: "however, the differences were not significant in the prehypertension group". This statement was not clear. Do you compare the differences between prehypertension with optimal BP group, or vs hypertension group? 5. Discussion: line 34: Furthermore, combined risk factors were more significant… risk factors for what? 6. Some language corrections are needed: P2, line 10 "was used" P9, line 11 "hypertension group" P9, line 14 "level"

	P12, line 52 "uric acid" could be "UA"

REVIEWER	Beatrice Baldinger Bern University Hospital, Switzerland.
REVIEW RETURNED	22-Sep-2014

GENERAL COMMENTS	Reference 10, 11 are incomplete. This a very well written descriptive study of risk factors for pre-hypertension defined in JNC 7, in Southern China. This is an important epidemiologic analysis and the topic could be of greater interest. But even so, I have some questions and concerns as follows. Major comments: > The authors discuss the incidence of pre-hypertension in the introduction that the incidence in Southern China has been rarely reported, but the study then describes the prevalences and associated risk factors. Do you mean prevalences instead of incidence in the introduction? > It should be cautious about including variables in multivariate analyses that may be in the same pathway, e.g. overweight/obesity--glucose--blood pressure. So multi-collinearity (strong correlations among independent variables) should be examined. > Did the authors consider looking more closely at age? Rather than dichotomizing to <50 and ≥50, it would be very interesting to see whether deciles of age influenced outcomes. > Treatment of prehypertenison is not recommended in the most recent published hypertension guidelines (JNC 8, 2013 ESC/ESH). How do the authors think the results fit with these guidelines? This could be mentioned in the discussion. Minor comments: > The ethical statement in Page 6, line 44 is redundant, as it is duplicated with the part of ethical clearance in Page 8. > Reference 10, 11 are incomplete.

REVIEWER	YURKOV ALEXANDR Moscow State University of Medicine and Dentistry, Moscow, Russia.
REVIEW RETURNED	24-Sep-2014

GENERAL COMMENTS	This study report that prehypertensive individuals presented with other risk factors associated with cardiovascular disease, such as overweight, dyslipidemia, impaired glucose, and hyperuricemia. Furthermore, combined risk factors were more significant in people with high-range prehypertension. This is the first study to show that there is a significant heterogeneity of combined risk factors within the prehypertensive subgroups. This paper is well written. I only have a few minor questions. It would be substantially more important if this study could include follow-up data about the progression of disease within the prehypertensive subgroups. However, the objective of exploring the relative heterogeneity of combined risk factors within the prehypertensive subgroups is of importance in itself. I would like to read their follow-up data in the future.

	Methods: The description for criteria of dyslipidemia is not well written and needed rewritten. 'Hyperuricemia was defined as … and 357 mol/L in women' It should be µmol/L. In Table 4, is the comparison group all who are not pre-HTN or Optimal BP? Please add some legends to this table. In P6, line 54, 'Normal BP' was used to define SBP < 120 mm Hg and DBP < 80 mm Hg, but in elsewhere, it is defined as optimal BP. Please keep the definition consistent. A conclusion paragraph is needed to help the readers to summarize the study easily.

REVIEWER	Yingxian Sun The First affiliated hospital of China Medical University
REVIEW RETURNED	01-Oct-2014

GENERAL COMMENTS	Hypertension is a worldwide public health problem. This is a meaningful retrospective study which reported the prevalence of pre-hypertension and associated risk factors in Shunde city, Guangdong province, the south of China. However, several serious issued of this study need to be addressed. Major comments 1. The study subject of this study is from a community-based checkup population which has poor representative. The choice of community-based checkup population has great selective bias, which may lead to the results invalid. 2. This is a retrospective study and we can't obtain the result of incidence of hypertension, yet the author really wrote "to explore the incidence…" in the objective. 3. What is the response rate of this study? 4. The protocol of blood pressure measurement should be written clearly: the model of sphygmomanometer? Electronic sphygmomanometer or mercury sphygmomanometer? How many times for blood pressure measurement for individuals? How about the quality control of blood pressure measurement? How to solve the digit preference and number preference of blood pressure measurement, etc. 5. Among the formulas for calculating the glomerular filtration rate by creatinine, CKD-EPI has been proved the best. 6. All of the risk factors found in this study are common ones. Given the representative of the sample is poor, if this study can be published in local journals, it will play a vital role in the prevention and treatment of the local public health.

Reviewer #1(Professor Kelsi Anderson):
1. Abstract-Design: The authors stated that this is "a cross-sectional study…. ". However, according to the methods in the main text, this is a retrospective study, using the community-based health checkup information.
Response: Thanks for the reviewer's comments. We had revised the abstract as "a retrospective study…. ". Thank you.

2. Method: "The study information was collected in the First People's Hospital of Shunde"…"This study was approved by the Ethics Committee of the Affiliated Hospital at Shunde of the Southern Medical University " Are the statements indicating the same hospital? If yes, please make the statements consistent.
Response: Yes. Both the names indicate the same hospital. We are sorry for the inconsistency and have revised it. Thank you.

3. Results: As presented in table 1, the prevalence of prehypertension in female with 50–64 years was 36.3%, and 34.4% in those with ≥ 65 years old. I think this is very similar, and maybe it is not proper to state that "there was an increasing trend of prehypertension prevalence associated with age in men, but in women, the prevalence of prehypertension increased up to the age of 50–64 years and then decreased",   especially in the case that linear correlation analysis was not performed.
Response: This is an important suggestion. We have revised this statement as "There was an increasing trend of prehypertension prevalence associated with age". Thank you.
4. Results: page 9, line 19: "however, the differences were not significant in the prehypertension group". This statement was not clear. Do you compare the differences between prehypertension with optimal BP group, or vs hypertension group?
Response: We are sorry for the unclear statement. We compared the differences between prehypertension with optimal BP group here. So we have revised this sentence as "however, the differences were not significant in prehypertension group compared with that in the optimal BP group". Thank you.

5. Discussion: line 34: Furthermore, combined risk factors were more significant… risk factors for what?
Response: It should be "combined cardiovascular risk factors were more significant…". We have revised this sentence. Thank you.

6. Some language corrections are needed:
P2, line 10 "was used"
P9, line 11 "hypertension group"
P9, line 14 "level"
P12, line 52 "uric acid" could be "UA"
Response: We are so grateful of the suggestions. We have gone through our manuscript and revised some editing of syntax, including which mentioned by the reviewer. Thank you.

Reviewer #2(Professor Beatrice Baldinger):

Major comments:
1. The authors discuss the incidence of pre-hypertension in the introduction that the incidence in Southern China has been rarely reported, but the study then describes the prevalence and associated risk factors. Do you mean prevalence instead of incidence in the introduction?
Response: How important of this comment. We are sorry for not stating this clearly in the prior

manuscript. In this study, we explore the prevalence of prehypertesion in Guangdong Province, southern China. We have revised the statement "incidence" as "prevalence" throughout the manuscript. Thank you very much.

2. It should be cautious about including variables in multivariate analyses that may be in the same pathway, e.g. overweight/obesity--glucose--blood pressure. So multi-collinearity (strong correlations among independent variables) should be examined.
Response: We appreciate the review's suggestion. According to this suggestion, we further performed multicollinearity analysis to examine whether the results are affected by strong correlations among independent variables. Variance inflation factor (VIF) values > 4.0 or tolerance < 0.25 may indicate concern for multicollinearity in multivariate regression models (Pallant J. SPSS survival manual: a step by step guide to data analysis using SPSS for windows (version 10). Open University Press; 2001). We found that collinearity statistics were >0.25 for tolerance and <3.5 for VIF, suggesting that multicollinearity was not a concern among the independent variables. We have added the methods and results in the manuscript. Thank you.

3. Did the authors consider looking more closely at age? Rather than dichotomizing to <50 and ≥50, it would be very interesting to see whether deciles of age influenced outcomes.
Response: This is also a very important suggestion. We have analyzed the association of prehypertension and deciles of age and still find that age is a risk factor of prehypertension. We have revised the results and table 4. Thank you.

4. Treatment of prehypertenison is not recommended in the most recent published hypertension guidelines (JNC 8, 2013 ESC/ESH). How do the authors think the results fit with these guidelines? This could be mentioned in the discussion.
Response: Thanks for the suggestion. In this study, we found that prehypertensive individuals presented with many other cardiovascular risk factors. There was heterogeneity of combined risk factors within the prehypertensive subgroups. These findings confirmed the importance of the definition of prehypertension, and was in accordance with our prior meta analysis, which found that prehypertension is associated with increased risks of composite CVD (BMC Med. 2013 ;11:177.), stroke (Neurology. 2014;82(13):1153-1161.), and end-stage renal disease (Am J Kidney Dis. 2014;63(1):76-83.). However, because of limit prospective, randomized trials examining the effects of anti-hypertensive therapy on reducing CVD specifically in prehypertensives, professional societies do not currently recommend pharmacotherapy for prehypertension, even in individuals with high-range prehypertension. So we think that there is a great gap to be covered between epidemiological studies and randomized controlled studies in prehypertension. Prehypertensive individuals are at a high risk to progress to sustained hypertension, as well as CVD and renal damage. So periodic screening is important. For therapeutic implications, we emphasize that lifestyle intervention, but not medical intervention is the mainstay of treatment for prehypertension. However, high-risk subpopulations with prehypertension are needed to be selected for future controlled trials of pharmacological treatment. We have discussed these points in the revised manuscript. Thank you.

Minor comments:
1. The ethical statement in Page 6, line 44 is redundant, as it is duplicated with the part of ethical clearance in Page 8.
Response: We have deleted this sentence. Thanks.

2. Reference 10, 11 are incomplete.
Response: We are sorry for not formatting the reference clearly. We have revised these references. Thank you.

Reviewer #3 (Professor YURKOV ALEXANDR):

1. It would be substantially more important if this study could include follow-up data about the progression of disease within the prehypertensive subgroups. However, the objective of exploring the relative heterogeneity of combined risk factors within the prehypertensive subgroups is of importance in itself. I would like to read their follow-up data in the future.
Response: Thanks for the reviewer's comments. We agree that it is important to evaluate the progression of disease within the prehypertensive subgroups in the future. Actually, follow-up of our study is being processing and we hope we can report the results in the future. Thank you.

2. Methods: The description for criteria of dyslipidemia is not well written and needed rewritten. 'Hyperuricemia was defined as … and 357 mol/L in women' It should be μmol/L.
Response: Thanks for these kind suggestions. We have revised these sentences in the methods.

3. In Table 4, is the comparison group all who are not pre-HTN or Optimal BP? Please add some legends to this table.
Response: We are sorry for not state this clearly in the prior manuscript. To evaluate predictive factors for prehypertension, individuals with optimal BP were used as reference. We have state this in the method, as well as in the legend of table 4. Thanks.

4. In P6, line 54, 'Normal BP' was used to define SBP < 120 mm Hg and DBP < 80 mm Hg, but in elsewhere, it is defined as optimal BP. Please keep the definition consistent.
Response: We are sorry for the in consistency of definition. It had been revised. Thanks.

5. A conclusion paragraph is needed to help the readers to summarize the study easily.
Response: This is a very important suggestion. A conclusion paragraph is added in the revised in the manuscript. Thank you.

Reviewer #4 (Professor Yingxian Sun):

1. The study subject of this study is from a community-based checkup population which has poor representative. The choice of community-based checkup population has great selective bias, which may lead to the results invalid.
Response: Thanks for the reviewer's comments. We have discussed in the limitation that our data were based on community-based health checkup information. However, our results showed that many other cardiovascular risk factors were presented in individuals with prehypertension. Furthermore, there was a significant heterogeneity of combined risk factors within the prehypertensive subgroups. We think these messages are valid and important for risk classification in prehypertension. Thank you.

2. This is a retrospective study and we can't obtain the result of incidence of hypertension, yet the author really wrote "to explore the incidence…" in the objective.
Response: We are sorry for not stating this clearly in the prior manuscript. In this study, we study the prevalence of prehypertesion in Guangdong Province, southern China. We have revised the statement "incidence" as "prevalence" throughout the manuscript. Thank you very much.

3. What is the response rate of this study?
Response: Thanks for the reviewer's comments. Our data were based on retrospective analysis of community-based health checkup information, so the response rate was not accessed in the setting. Thank you.

4. The protocol of blood pressure measurement should be written clearly: the model of sphygmomanometer? Electronic sphygmomanometer or mercury sphygmomanometer? How many

times for blood pressure measurement for individuals? How about the quality control of blood pressure measurement? How to solve the digit preference and number preference of blood pressure measurement, etc.

Response: Thanks for these suggestions. Although our data were based on retrospective analysis of community-based health checkup information, the protocol of blood pressure measurement in our Health Management Center are carried out consistently since the foundation of the department. We have introduced the protocol in the method.

5. Among the formulas for calculating the glomerular filtration rate by creatinine, CKD-EPI has been proved the best.

Response: Thanks for the reviewer's comments. We agree that in some studies, CKD-EPI has been proved the best to access eGFR. However, most of these studies were based on patients with CKD, but not from general participants. Second, the CKD-EPI had not been modified in Chinese. So in this study, we used the modified MDRD equation adapted for Chinese in our study, we think the choice of which formula is not an obstacle for analysis in our study. Thank you.

6. All of the risk factors found in this study are common ones. Given the representative of the sample is poor, if this study can be published in local journals, it will play a vital role in the prevention and treatment of the local public health.

Response: Thanks for the reviewer's positive comment that our study will play a vital role in the prevention and treatment of the local public health. However, as commented by the first reviewer, although data are from a geographic area, it is relevant for most clinicians worldwide, and the findings may have implications for decision-making in relation to prevention of hypertension and cardiovascular disease. So we hope to publish this paper in an international journal. Thank you.

VERSION 2 – REVIEW

REVIEWER	Kelsi Anderson School of Public Health, Baylor College of Medicine
REVIEW RETURNED	17-Oct-2014

GENERAL COMMENTS	The authors have addressed all my comments. I have no further comments to add on this manuscript.

REVIEWER	Beatrice Baldinger Swiss Cardiovascular Center, Bern University Hospital, Switzerland.
REVIEW RETURNED	19-Oct-2014

GENERAL COMMENTS	I have reviewed this new version. It looks very good now. The authors have incorporated all major suggestions provided by reviewers.